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ORIGINAL PAPER

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Cerebral networks linked to the event-related potential P300

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Abstract P300 is an event-related potential that is elicited by an oddball paradigm. In several neuropsychiatric diseases, differences in latencies and amplitude compared to healthy subjects have been reported. Because of its clinical significance, several investigations have tried to elucidate the intracranial origins of the P300 component. In the present study we could demonstrate a network of P300 generators. Investigated were 15 healthy subjects with an acoustical oddball paradigm within a fMRI block design, which enabled us to exclude attention or acoustical processing effects. The inferior and middle frontal, superior temporal, lower parietal cortex, the insula and the anterior cingulum were significantly activated symmetrical in both hemispheres.

Key words P3 · P3 generators · event related potentials · oddball paradigm · working memory

Introduction

Oddball tasks involve the presentation of rare target stimuli amongst more frequently occurring non-target stimuli. Electrophysiologically it elicits an event-related potential (ERP) component called P300, occurring around 300 ms after stimulus onset (Sutton et al. 1965). Compared to earlier components of the ERP, the P300 depends on cognitive, memory and attentional functions. Therefore it was used to investigate in several neuropsychiatric diseases like schizophrenia. In schizophrenia a general but non-specific amplitude reduction of the P300 component was repeatedly demonstrated (Strik et al. 1994; Ford et al. 1994). Amplitude reductions could also be shown in major depression and alcoholism (Müller et al. 2001). A more specific finding in schizophrenia is the dislocation of the topographical P300 maximum to the right (Strik et al. 1994). This dislocation seems to be correlated to volume reduction in the left temporal superior gyrus (McCarley et al. 2002). But not all studies could confirm the general topographic shift to the right (Iwanami et al. 2002). Furthermore the P300 component correlates with the degree of formal thought disorder (Iwanami et al. 2000; Frodl et al. 2002) and the disorganisation syndrome (Higashima et al. 1998) in schizophrenia. Moreover latency prolongations have been fond in Alzheimer's dementia, borderline personality disorder, alcoholism and sometimes also in schizophrenia (Müller et al. 2001).

Searching for the underlying pathomechanism of P300 abnormalities in schizophrenia and other diseases, a central issue is to determine which cerebral structures are involved in the generation of P300. There have been several approaches to localize the generators using dipole source modeling from EEG/MEG data (Tarkka et al. 1995; Hegerl and Frodl-Bauch 1997), intracranial recordings (Halgren et al. 1995a; Halgren et al. 1995b) and fMRI methods (Menon et al. 1997; McCarthy et al. 1997; Linden et al. 1999). In summary, previous studies allocated the P300-generation to a broad network of regions in frontal, temporal and parietal cortex. However these studies did not differentiate between general paradigm-related activations and activations more specific for the P300 component. Oddball tasks evoking a P300 require focused attention and information preprocessing of the acoustical or visual presented stimuli during the whole task. These different processes can be separated in electrophysiological studies due to the high temporal resolution of these methods. FMRI due to its

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low temporal resolution can not easily separate these components. The aim of the present study was to map P300 generators by fMRI excluding focused attention and information preprocessing effects and at the same time retain the activations more specifically related to the P300 generation. To achieve this, we used three different epoch categories (blocks) within an fMRI block design study: 1) no stimulation, 2) stimulation only by the non-target stimuli, and 3) stimulation with non-target and target stimuli. Subjects were not informed about the occurrence of epochs (blocks) without target stimuli and therefore always expected the target stimulus. The effects of focused attention and information preprocessing are the same in the two epoch categories with stimulation. Therefore brain regions showing activity only in the epochs with target stimulation should be devoid of effects generated by focused attention and information preprocessing.

Method

Subjects

A total of 15 subjects (3 female, 12 male) participated in the study. Mean age (± standard deviation; SD) was 28 ± 6 yrs. Only subjects without neurological or psychiatric disturbances or reduced hearing were included. The study was approved by the local ethics committee. All subjects gave their informed consent to participate in the study and reported being free of any psycho-active medication.

Equipment

fMRI measurements were performed on a 1.5 Tesla Magnetom Vision (Siemens, Erlangen, Germany) and the functional measurements were acquired using commercially available echo-planar-sequences from Siemens (TR: 4000ms, TE: 69 ms, matrix: 128x128, mean FOV 210 mm). Since maximal 15 axial slices could be acquired in one volume, 2 series of measurements were necessary to cover the whole brain. The slices were placed parallel to the AC-PC line on a midsagittal scout, had a thickness of 4 mm (1 mm interslice distance) for the upper and 3 mm (0.75 mm interslice distance) for the lower functional series. The slices were acquired in pseudo random order. Additional to functional acquisitions T1 weighted anatomical measurements were performed with the same slice positions as for the functional measurements (matrix 256x256; TE: 12 ms; TR: 400 ms). For 3-dimensional anatomical registration a T1 (TE: 5ms, TR: 30ms) weighted sequence with a spatial resolution of 1 mm was used.

Stimulation

FMRI was performed using a block design with 3 different epoch categories, each 32s long. 1) Epochs without acoustical stimulation, 2) epochs consisting of one tone (4000 Hz), and 3) epochs consisting of two tones (1000 Hz and 4000 Hz) (see Fig. 1). In epoch category 2 and 3 the stimulus frequency was 1/s. The tone duration was 100ms. The acoustic stimuli were presented by tape recorder with an air pressure acoustical system to avoid influences on the magnetic field. The loudness of the tones was chosen to allow a clear discrimination between the stimuli during the functional scanning (95 dB). The sound of the scanner noise was damped by custom made earphones, reducing the noise of the scanner about ~30 dB (Di Salle et al. 2001). Prior to the functional measurement subjects were instructed to pay attention to the 1000 Hz tone (target stimulus) and to ignore the 4000 Hz tone (nontarget stimulus). The subjects were not informed that there will also be epochs consisting only of non-target tones (epoch category 2). Commonly the instruction in a P300 paradigm includes a motoric or arithmetic response to the target stimulus. However, since any interference of brain activity exclusively related to a motoric or arithmetic response was to be avoided no such instruction was given. The subjects were tested electrophysiologically before the fMRI session using an oddball paradigm comparable to epoch category 3 in the fMRI measurement. Only subjects who had a clear electrophysiological P300 response using this aforementioned P300 paradigm were included in the study (15 out of 20 subjects). The motoric activity during the fMRI measurement was controlled by simultaneous surface EMG recorded from both wrists. No increased activity could be seen during the fMRI measurement.

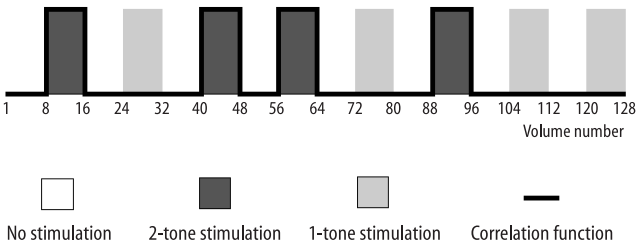

Fig. 1 The experimental tasks during one fMRI-run are shown. The 3 different task epochs are symbolized by the background color. The correlation function used for extracting P300 related activity from activity related to other evoked potentials is displayed by the black line

This stimulation protocol enabled us to differentiate between activations due to acoustical activations in general and activations related to the P300 activity. In epoch category 3 the ratio between target and non-target stimuli was 1:3. Each fMRI measurement consisted of total 16 epochs (8 min and 32 s): 4 of the non-target and 4 target epoch categories and 8 of the no-tone category. A total of 128 volumes were acquired. The epoch categories were presented in random order to avoid habituation effects.

Data analysis

All imaging data were processed using the Software Brain-Voyager (BrainInnovation BV, Maastricht, Netherlands). Regions of interest (ROI's) were determined by a data driven approach correlating the measured signal time course in each voxel with a boxcar function corresponding to the epoch categories (Fig. 1). The first volume of each measurement was disregarded due to T1 saturation effects. Epochs of the category 1 and 2 were set to 0, whereas epochs of the category 3 containing target tones were set to 1 in the boxcar function. Voxels showing an increased signal during epoch category 3 and not during the other epoch categories were expected to show the highest correlation value. Thus for each voxel in each slice a correlation coefficient was calculated. Only 8 ROI's in each hemisphere with the highest correlation coefficients in all subjects were included in further analysis.

Anatomical analysis

The ROI's were localized in the normalized Talairach space for each subject and allocated to the corresponding Brodmann area and the Talairach coordinates were used for calculation of mean activation coordinates for the whole study population.

Statistical analysis

The mean time signal intensity curves over all voxels in each ROI were standardized. All epochs of the same epoch category the signal intensity were averaged. For averaging only the 3rd to 8th volume of each epoch was used to avoid the initial overshoot of the BOLD effect and to allow the signal to reach a stable equilibrium after a possible acti-

vation. For final overall statistical analysis a repeated measurement ANOVA for the factors epoch category (no-tone, non-target, and target epoch), laterality, and anatomical region (Brodmann area) was calculated. The post hoc comparison was also done by ANOVA.

Results

The following 8 Brodmann areas were determined as ROI's in all subjects: BA 9, precentral gyrus, BA 45/46, BA 24/32 (anterior gyrus cingulum) and supplementary motor area (SMA) in area 6 in the frontal lobe, in the parietal lobe, BA 40, finally insula and BA 22 in the temporal lobe (Fig. 2).

The repeated measurement ANOVA for the factors epoch category (no-tone, non-target, and target epoch), laterality, and anatomical region (Brodmann area) resulted in non-significant effects of the factor region ($F(7.77) = 1.62$; $p > 0.10$). The factor epoch category ($F(2.22) = 123.24$; $p < 0.01$), the factor laterality ($F(1.11) = 5.93$; $p < 0.05$) and the interaction between region and epoch category ($F(14.154) = 1.83$, $p < 0.05$) gained statistical significant effects. Post hoc analysis for the factor epoch category showed that the difference between the target and non-target tone ($F(1.5) = 368.90$; $p < 0.01$) and the no-tone category and the target tone ($F(1.5) = 467.37$; $p < 0.01$) were significant contributing to the overall significant result. The difference between the non-target and no-tone category was insignificant ($F(1.5) = 6.49$; $p < 0.10$) but showed a trend. The significant interaction between the factors region and epoch category indicated that the activation levels for epoch categories varied in the different regions. The mean coordinates of the activation in the Talairach space for all subjects for the 8 ROI's were calculated (Table 1).

Discussion

In the literature, many cerebral areas have been considered to be the source of the scalp P300. Consistent with recent studies the present study suggests multiple generators in widespread cortical areas and deeper structures to be involved in the generation of the scalp P300 (Ebmeier et al. 1995; Halgren et al. 1998).

Compared to our previous study using event-related fMRI (Linden et al. 1999) we now found an extended network including additional areas due to the fact what the entire brain was scanned; therefore both studies complement each other. Furthermore the present study can exclude influences of side effects of P300 paradigms like information preprocessing and focused attention due to the three epoch category stimulation design.

According to the hypotheses about the functional importance of P300, it represents a process in the working memory system (Donchin and Coles, 1988). Most of the regions found in the present study have been demonstrated to be activated in working memory studies previously. One of these regions is the inferior parietal cortex (BA40) (Pardo et al. 1991; Owen et al. 1996; Smith et al. 1996; Fiez et al. 1996; Cohen et al. 1997). The attribution of BA 40 to the phonological loop of the working memory system has been shown in PET studies (Petrides et al. 1993). Several studies with intracranial recordings (Richter et al. 1989; Halgren et al. 1995a) and also studies with fMRI (Menon et al. 1997; McCarthy et al. 1997; Linden et al. 1999) have been able to demonstrate the importance of this region for the generation of P3. Unilateral temporal-parietal lesions markedly reduced P300 responses to all types of infrequent stimuli, supporting the notion that BA 40 plays a critical role in scalp P300 generation (Yamaguchi and Knight, 1991).

The involvement of the dorsolateral prefrontal cortex in working memory has been shown across a number of functional imaging studies (Petrides et al. 1993; Owen et al. 1996; Smith et al. 1996; Cohen et al. 1997) and seems to be relatively independent of the experimental paradigm (Fiez et al. 1996). Also studies of the phonological loop showed activation of this region (Petrides et al. 1993). As suggested by Fiez et al. (1996) based on results of other studies the left frontal operculum is a region where the Broca area is integrated. This region might participate not only on specific aspects of subvocal rehearsal but also on other tasks of phonological and acoustic paradigms like the oddball task.

In a study using regional cerebral blood flow evidence was found for the participation of BA 45/46 in generation of P300 (Ebmeier et al. 1995). Furthermore studies using intracranial recordings confirmed the involvement of the prefrontal cortex in the generation of

Table 1 Average Talairach coordinates (x/y/z) for the significant activated brain-regions over all subjects. The BA 24/32 (anterior Cingulum) and the SMA (in BA 6) were considered as midline activations. They were always symmetrical in both hemispheres. The symmetrical activation in both hemispheres was considered as one entity. For the average coordinates they have been considered as one

	right			middle			left		
	x	y	z	x	y	z	x	y	z
BA 22	58.5	−34.6	11.2				−58.2	−23.7	6.9
BA 40	53.6	−41.3	33.6				−52.3	−40.8	33.3
BA 45/46	45	25.3	12.4				−43.2	27.3	13.9
GPRC	44.5	−1.4	40.4				−43.6	−0.64	38.9
BA 9	39.7	29.3	33.3				−35.7	28.9	34.3
Insula	35.9	12.5	3.4				−35.3	12.4	6.4
BA 24/32				−0.6	12.3	35.7			
SMA				−1.2	−0.9	58.3			

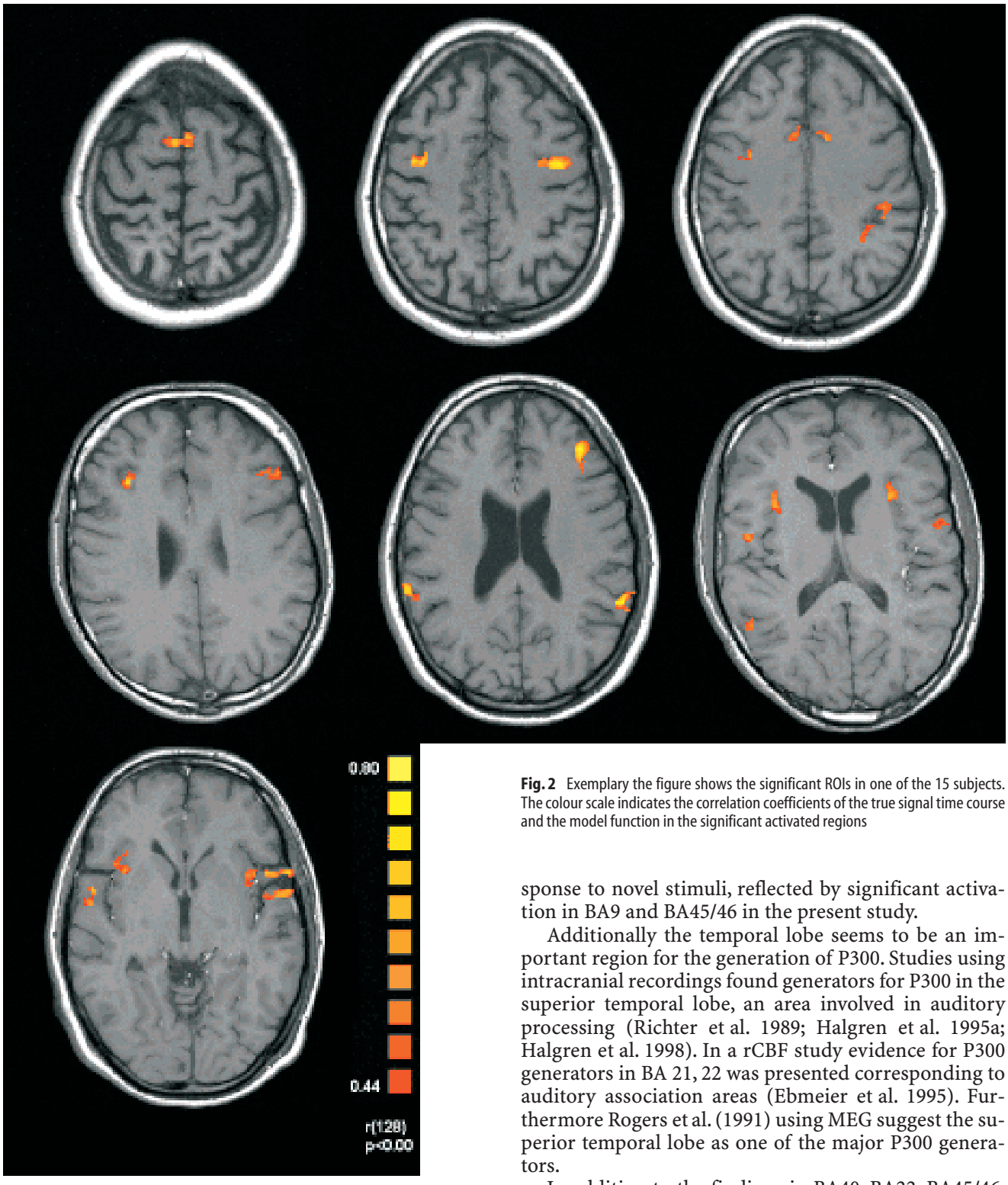

Fig. 2 Exemplary the figure shows the significant ROIs in one of the 15 subjects. The colour scale indicates the correlation coefficients of the true signal time course and the model function in the significant activated regions

P300 (Halgren et al. 1998). Patients with prefrontal lesions showed no fronto-central P300 response to target stimuli compared to control subjects (Knight, 1984). BA 45 has also been previously demonstrated to be active in P300-fMRI studies (Linden et al. 1999). These results indicate that the prefrontal cortex is essential for the response to novel stimuli, reflected by significant activation in BA9 and BA45/46 in the present study.

Additionally the temporal lobe seems to be an important region for the generation of P300. Studies using intracranial recordings found generators for P300 in the superior temporal lobe, an area involved in auditory processing (Richter et al. 1989; Halgren et al. 1995a; Halgren et al. 1998). In a rCBF study evidence for P300 generators in BA 21, 22 was presented corresponding to auditory association areas (Ebmeier et al. 1995). Furthermore Rogers et al. (1991) using MEG suggest the superior temporal lobe as one of the major P300 generators.

In addition to the findings in BA40, BA22, BA45/46, BA9, the anterior cingulate appears to be critically involved in target detection (Posner et al. 1988). These findings of the anterior cingulate region in the present study are consistent with intracranial recordings indicating the presence of large electrical potentials and polarity inversions to target stimuli in the range of the P300 latency (Baudena et al. 1995). This region was also

found in a regional blood flow study with an oddball task (Ebmeier et al. 1995). A combined study with fMRI and EEG/dipolanalysis suggested that the anterior cingulate is a major generator of the P300 component (Menon et al. 1997). This has been confirmed by other studies (Linden et al. 1999).

The activation in the insular cortex in an oddball paradigm was previously demonstrated by MEG and EEG/dipolanalysis (Tarkka et al. 1995). In studies about selective attention the insula was also found to be active (George et al. 1994). Fiez et al. (1996) suggested that the insular region is involved primarily in the production of overlearned, relatively automatic responses. But still the role of the insula in target detection and especially in the P300 generation remains uncertain although it could be demonstrated in previous P300-fMRI studies (Linden et al. 1999).

The activations in BA 6 (SMA and lower precentral gyrus) are intriguing due to the missing motor task. One possible explanation is that these activations were the result of movement planning by the subjects in the moment monitoring the target tone. One other possibility is to interpret the activations in BA 6 (SMA and gyrus praecentralis (GPRC)) as a part of the working memory system; a hypothesis supported by previous studies (Fiez et al. 1996; Cabeza and Nyberg 1997). Concerning the activation in the SMA the results of Fiez et al. (1996) show that the SMA is activated in working memory paradigms which did not include a motor task. Activation of this region in oddball tasks were demonstrated before (Linden et al. 1999).

Studies using various techniques (intracranial recordings, MEG, EEG/dipole analysis) suggest the hippocampal formation as one of the possible generators (Tarkka et al. 1995). In spite of these results it is not clear to what degree the hippocampal P300 contributes to the scalp P300. Studies of P300 following unilateral anterior lobectomy (including hippocampus) in humans have failed to show any related change in the scalp P300 amplitude (Stapleton et al. 1987). Bilateral hippocampal lesions in humans did not impair performance in this task (Polich and Squire, 1993). Other functional imaging studies about P300 generators in line with the present study could not find activation of the hippocampus (Menon et al. 1997; McCarthy et al. 1997). We can not exclude that the missing activation of the hippocampal formation in the present study is a result of measurement difficulties resulting from susceptibility artifacts in this region. However considering the above mentioned lesion-studies the hippocampus seems to have no crucial role for the generation of the scalp P300.

A limitation of the present study is that fMRI can not monitor electrical activity directly. It is based on BOLD changes due to a regional change of oxygen consumption. The BOLD signal is proportional to the regional amount of active neurons (Rees et al. 2000). The generation of electrical potentials comprises neuronal activity and therefore also should evoke a BOLD signal change. However fMRI has a time resolution of several seconds. This temporal resolution does not allow the separation of events in a temporal scale of milliseconds like event-related potentials. In the present study we tried to overcome this problem by subtracting non-targets from targets, which should debar activations due to focused attention and information preprocessing. But still it remains unclear, whether the activations showed here are all generators of P300. All presented activations should be specific for target detection, but the P300 component is only a part of the target detection mechanism. Therefore we have to use additional information provided by electrophysiological studies especially by intracranial recordings to verify the linkage of the fMRI activations to the generation of P300. Activations in regions without confirmation by intracranial recordings can be attributed to the target detection network but not unambiguously as a P300 generator. Unfortunately intracranial recordings studies have only been performed in a very limited number of brain regions due to the positions of implanted electrodes. Non-invasive electrophysiological methods for source localization of evoked potentials do not provide unambiguous results due to the inverse problem (Nunez and Silberstein, 2000). A promising approach to minimize the mentioned problems of source localization might be the combination of fMRI and simultaneous EEG-recordings in future investigations (Horwitz and Poeppel, 2002).

Conclusion

The present and previous investigations suggest that most of the cerebral areas involved in the P300 generation have been determined. The localization of the generator network of P300 supports the hypothesis about a functional process in the working memory system suggested by the functional hypothesis of P300 (Donchin and Coles, 1988). We believe that on the basis of our results future clinical P300 research may now be able to draw conclusions about disturbed cerebral structures involved in neuropsychiatric diseases.

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